REMARKS

Claims 1-41 are pending in the application. Claims 19, 20 and 34-41 are withdrawn from consideration. Claims 5 and 6 were withdrawn from consideration as being drawn to non-elected species claims. Claims 2 and 10-18 are allowed. Claims 1, 3-9 and 21-33 are rejected. By virtue of this amendment, claims 1 and 24 are canceled and claims 3, 7, and 21-23 are amended. Accordingly, claims 2-18, 21-23 and 25-33 are currently under consideration.

Rejections are levied under Section 112, 2d paragraph (indefiniteness), Section 112, first paragraph (written description and enablement) and Section 102. Applicant notes that the Examiner did not state that the outstanding rejections of claims 1-18 and 21-31 under Section 112 (enablement), claims 1,2, 8, 21-23 under Section 112, second paragraph (indefiniteness), claims 1, 3, and 4 under Section 102 (over Ling et al.) and claims 1, 2-4, 7, 14-18, 21-24, and 29-33 under Section 102 (over Spielmann et al.) are withdrawn, but did not re-levy these rejections. Thus, these rejections do not apply to the claims 1-41 as pending before entry of this amendment. The Examiner has maintained the rejection of claims 1, 3-5, and 7 under Section 102 over the Wobus reference.

With respect to all amendments and cancelled claims, Applicant has not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicant reserves the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional application.

Request for rejoinder of withdrawn species claims

Applicant notes that claims 5 and 6 were withdrawn from consideration as drawn to non-elected species. Applicant respectfully requests rejoinder of the withdrawn species claims upon allowance of a claim that encompasses the currently withdrawn species.

Interview and Information Disclosure Statement

Applicant thanks the Examiner for extending the courtesy of the helpful telephone interview with Applicant's representative, on July 10, 2002 with Primary Examiner Reynolds. This response reflects the results of that interview.

Applicant gratefully acknowledges the receipt of the initialed Form 1449s (paper nos. 8 and 18). Applicant notes that one additional Supplemental Information Disclosure Statement was submitted on March 20, 2002. Applicant would appreciate it if the Examiner could review the references and initial and return the 1449 submitted therewith.

Claim Rejections Under 35 U.S.C. § 112, second paragraph (indefiniteness)

Claims 1 and 3-9 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicant respectfully traverses this rejection.

Claim 1 has been canceled and claims 3-9 have been amended so that they do not depend from claim 2. Accordingly, this rejection is moot. Withdrawal of this rejection is respectfully requested.

Claim Rejections Under 35 U.S.C. § 112, first paragraph(written description)

Claims 1, 3-9 and 24 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant respectfully traverses this rejection for the following reasons.

1. Claims 1 and 3-9

Claim 1 and 3-9 is rejected under Section 112, first paragraph, for reciting the term "unmodified". As noted above, claim 1 has been canceled and claims 3-9 have been amended so

that they do not depend from claim 2. Accordingly, this rejection is moot. Withdrawal of this rejection is respectfully requested.

2. Claim 24

Claim 24 is rejected under Section 112, first paragraph, for reciting the phrase unknown test compositions. Applicant respectfully traverses this rejection.

Claim 24 has been canceled, and claims 21-23 have been amended to recite that the test chemical composition is "suspected of toxicity". Applicant believes that these amendments address the Examiner's concern. During the interview, Primary Examiner Reynolds reacted favorably to these amendments. Withdrawal of this rejection is respectfully requested.

Claim Rejections Under 35 U.S.C. § 112, first paragraph (enablement)

Claims 21-33 are rejected under 35 USC Section 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant respectfully traverses this rejection.

Claim 24

The Examiner asserts that because the specification allegedly fails to describe the "unknown test chemical composition" of claim 24, one of ordinary skill "would not known how to type or rank the toxicity of the unknown test chemical composition by using the claimed methods." Office Action, page 5. Applicant respectfully traverses this rejection. As noted above, claim 24 has been canceled, thus mooting this rejection. Withdrawal of this rejection is respectfully requested.

Claims 21-33

Claims 21-33 are rejected because the specification allegedly fails to provide adequate guidance and evidence for ranking or typing toxicity of a chemical composition. Applicant traverses this rejection.

Applicant submits that the specification fully enables the use of molecular profile data to type toxicity. See, e.g., specification at pages 26-30 (see especially page 26, lines 15-25 and pages 28), Examples 2 and 3, and Figures 2-4. For example, as discussed during the interview and described in Examples 2 and 3, Figures 2-4 display molecular profile data obtained from EBs treated with troglidazone and erthythromycin, two drugs with known liver toxicity. Inspection of the molecular profile data reveals that the patterns of alteration (between test chemicals and the control EB, shown in panel A) are similar. Moreover, as discussed in the Example (see specification at, e.g., page 34-35), there are at least 5 bars shown in Figure 2 with expression levels that are altered (increased or decreased) in the test EBs verses the control EBs. Thus, each bar is a candidate marker for a protein that is expressed in response to drugs with potential liver toxicity. As noted by the Primary Examiner in the interview, these data indicate that patterns of alterations in molecular profiles are "findable" when comparing the molecular profiles of EBs treated with a test chemical composition verses control EBs, respectively. *See also* Figures 3 and 4, and Example 3. In Example 2 and Figure 2-4, test chemical compounds that exhibit liver toxicity are exemplified. In Example 3, test chemical compositions that exhibit developmental toxicity are exemplified.

The specification also teaches that molecular profile data can be used to rank toxicity. As noted in the last response, "ranking toxicity" generally refers to determining a relative order (or rank) of chemical with respect to severity of the toxicity of the chemicals. As taught in the specification, once a molecular profile of a test chemical composition is prepared, it can be compared to that of a chemical composition with predetermined toxicities. The outcome of such comparison provides information for one to predict the likelihood of how toxic the test chemical composition is as compared to the other known toxic compositions. *See* specification at page 27. It is well-known in the art that toxicity can be ranked by a comparison of the dose of a test chemical that is necessary to achieve the particular biological effect that the toxicity assay measures (in the case of the present application, that would be the molecular profile, or the pattern of gene and/or protein expression measured in the EBs). Applying this information to the

data in Example 2, one sees that similar molecular profiles were collected from EBs treated with 50 uM of erthythromycin and 20 uM of troglitazone, respectively. Using this information, one of ordinary skill could rank erythromycin as less toxic than troglidazone because the concentration of erythromycin that results in production of the molecular profile is lower than the concentration of troglidazone that results in production of the molecular profile, or the pattern of alterations in expression between drug-treated and control EBs. Accordingly, Applicant submits that the specification fully enables the use of molecular profile data to rank toxicity. Withdrawal of this rejection is respectfully requested.

Applicant further notes that methods of comparison and correlation are well known and routinely used, and the guidance provided in the specification is more than adequate to allow one of ordinary skill in the art to carry out the invention. For example, the specification teaches that the comparison of gene or protein expression with toxicities can be performed by any convenient means, including visual comparison of patterns to determine patterns associated with different types of toxicity, database programs or neural networks, or informatics programs such as Spot-Fire or Gene Spring. See, e.g., the specification at page 26, line 1 through page 27, line 2; page 29, lines 4-21; Example 2-3 (passim).

The law is clear that to satisfy the enablement requirement, the specification must provide sufficient guidance regarding how to make and use the invention to allow the ordinarily skilled artisan to carry out the invention without undue experimentation. The law is clear that a specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as satisfying the enablement requirement unless there is reason to doubt the objective truth of the teachings of the specification. *In re Marzocchi*, 169 USPQ 367,369 (CCPA 1971). It is incumbent upon the Examiner to explain why one skilled in the art would doubt the truth of statements made in the specification, and provide back up assertions with acceptable and specific evidence. *Id.* at 370. Absent evidence to the contrary, the specification must be assumed to be enabling.

The Examiner has not met his burden of advancing acceptable and specific evidence in support of the enablement rejection. For example, the Examiner bases the rejection on the assertion that "different chemical compositions could result in very different and irregular molecular profile of gene or protein expressions" (Office Action, page 5), but the Examiner does not offer any authority or evidence in support of this assertion. The Examiner further states that the specification allegedly fails to provide correlation between pattern of gene or protein expression in a mammalian EB treated with a chemical composition, and the toxicity of a the chemical composition, and that in the absence of such a "correlation set", undue experimentation is required to practice the invention. Office Action, page 6. However, the Examiner does not provide acceptable evidence in support of this requirement, nor does the Examiner explain why the alleged lack of correlation data constitutes undue experimentation. Accordingly, it is evident that a *prima facie* case of enablement has not been made. Withdrawal of this rejection is respectfully requested.

Claim Rejections Under 35 U.S.C. § 102

Claims 1, 3-5 and 7 remain rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Wobus et al. (U.S. Patent No. 6,007,993, 1999, effective filing date of 2/24/98). Applicant respectfully traverses.

Claim 1 has been canceled and claims 3-9 have been amended so that they do not depend from claim 2. Accordingly, this rejection is moot. Withdrawal of this rejection is respectfully requested.

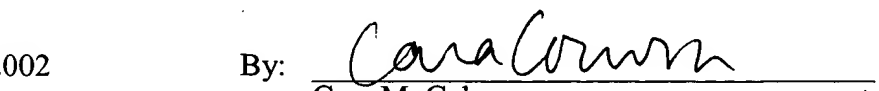
CONCLUSION

In light of the Amendments and the arguments set forth above, Applicant earnestly believes that they are entitled to a letters patent, and respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

In the unlikely event that the fee transmittal is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 441472000100.

Respectfully submitted,

Dated: July 24, 2002

By: 

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Please amend claims 3, 7, and 21-23.

3. (Amended) The method of claim [1 or] 2, wherein the alterations in gene expression or protein expression are detected by a label.

7. (Amended) The method of claim [1 or] 2, wherein the molecular profile comprises alterations in protein expression.

21. (Amended) A method of typing toxicity of a test chemical composition suspected of toxicity, comprising the steps of:

a) creating a molecular profile of the test chemical composition suspected of toxicity, comprising the steps of:

i) contacting an isolated mammalian embryoid body with the chemical composition; and

ii) detecting and recording alterations in expression of sets of genes or proteins in the mammalian embryoid body in response to the chemical composition compared to expression of sets of genes or proteins in an embryoid body not contacted with the chemical composition, to create a pattern of alterations in gene expression or protein expression; and

b) comparing the molecular profile in step a) with the molecular profile of a chemical composition having predetermined toxicities;

wherein the type of toxicity of the test chemical composition, if any, is determined by the comparison in step b).

22. (Amended) A systematic method of typing toxicity of a test chemical composition suspected of toxicity, comprising the steps of:

a) creating a molecular profile of the test chemical composition suspected of toxicity, comprising the steps of:

i) contacting an isolated mammalian embryoid body with the chemical composition; and

ii) detecting and recording alterations in expression of sets of genes or proteins in the mammalian embryoid body in response to the chemical composition compared to expression of sets of genes or proteins in an embryoid body not contacted with the chemical composition, to create a pattern of alterations in gene expression or protein expression; and

b) comparing the molecular profile in step a) with a composite library of molecular profiles of chemical compositions having predetermined toxicities, wherein the composite library comprises the molecular profiles of at least two chemical compositions, wherein said molecular profiles are created according to claim 2;

wherein the type of toxicity of the test chemical composition, if any, is determined by the comparison in step b).

23. (Amended) A method of ranking toxicity of a test chemical composition suspected of toxicity, the method comprising:

a) creating a molecular profile of the test chemical composition suspected of toxicity, comprising the steps of:

i) contacting an isolated mammalian embryoid body with the chemical composition; and

ii) detecting and recording alterations in expression of sets of genes or proteins in the mammalian embryoid body in response to the chemical composition compared to expression of sets of genes or proteins in an embryoid body not contacted with the chemical composition, to create a pattern of alterations in gene expression or protein expression; and

b) comparing the molecular profile in step a) with a composite library of molecular profiles of chemical compositions having predetermined toxicities, wherein the composite library comprises the molecular profiles of at least two chemical compositions, wherein said molecular profiles are created according to claim 2;

wherein the toxicity of the test chemical composition, if any, is ranked by the comparison in step b).